UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

10

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/315,292 | 05/20/99 | BENNETT C | ISIS-3561 |

HM12/0119

WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS
ONE LIBERTY PLACE-46TH FLOOR
PHILADELPHIA PA 19103

| EXAMINER | |
|---|---|
| SHIBUYA,M | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | 12 |

**DATE MAILED:** 01/19/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**



U.S. G.P.O. 1999 460-693

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/315292 | BENNETT ET AL | |
| | Examiner | Art Unit | |
| | Mark Shibuya | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)[·] Responsive to communication(s) filed on *26 October 2000* .

2a)[·] This action is **FINAL**. 2b)[ ] This action is non-final.

3)[ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)[·] Claim(s) *37-59,61,63 & 64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)[ ] Claim(s) _____ is/are allowed.

6)[·] Claim(s) *37-59,61,63 & 64* is/are rejected.

7)[ ] Claim(s) _____ is/are objected to.

8)[ ] Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)[ ] The specification is objected to by the Examiner.

10)[ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

11)[ ] The proposed drawing correction filed on _____ is: a)[ ] approved b)[ ] disapproved.

12)[ ] The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)[ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)[ ] All b)[ ] Some * c)[ ] None of:

1.[ ] Certified copies of the priority documents have been received.

2.[ ] Certified copies of the priority documents have been received in Application No. _____ .

3.[ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)[ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

15)[X] Notice of References Cited (PTO-892)
16)[ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)[ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
18)[ ] Interview Summary (PTO-413) Paper No(s) _____
19)[ ] Notice of Informal Patent Application (PTO-152)
20)[ ] Other:

## DETAILED ACTION

### *Response to Arguments*

1. The applicant's response filed 10/26/00 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 5/24/00 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

### *Information Disclosure Statement*

2. The information disclosure statement filed 4/3/00, with regards to reference AA, (Agrawal et al.), continues to fail to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The remainder of the IDS has been placed in the application file, but the information referred to therein in regard to reference DC, (Agrawal et al.) has not been considered.

3. As stated in the previous Office action, the following U.S. Application Serial Numbers have been considered: Reference LF, 08/383,666; LH, 08/465,880; LI, 08/468,037; LL, 09/009,490; LN, 09/044,506; LP, 09/071,433. Although these applications have been considered, reference to them on the PTO-1449 has been removed as failing to comply with 37 CFR 1.98 because they do not have publication dates. The following U.S. Application Serial Numbers were not available to the examiner and have not been considered: Reference LG 08/398,901; LJ, 08/762,488; LK, 08/777,266; LM, 09/016,520; LO, 09/062,416. These application will be

considered as they become available to the examiner. Reference LJ, 08/762,488 appears to have been cited in error by applicant, because the application is from an non analogous field of art.

4. In reference to the IDS filed 12/06/00, and as stated in the previous Office action, the following U.S. Application Serial Numbers have been considered: Reference OH, 08/383,666; ON, 09/009,490; OS, 09/071,433. Although these applications have been considered, reference to them on the PTO-1449 has been removed as failing to comply with 37 CFR 1.98 because they do not have publication dates. The following U.S. Application Serial Numbers were not available to the examiner and have not been considered: Reference OI, 08/398,901. This application will be considered as they become available to the examiner.

a. An updated copy of the IDS filed 4/4/00, reflecting new initialing by the examiner of considered references, is attached hereto.

***Claim Objections***

5. Claims 38 and 50 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Dependent claims 38 and 50 merely repeat limitations already found in independent claim 37, (from which claims 38 and 50 depend).

***Double Patenting***

6. Claims 37-59, 61, 63 and 64 were provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 37-61 of copending Application No. 09/083,586. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

a. This rejection is maintained for the reasons of record as set forth in the previous rejection mailed 5/24/00

b. In the response to the previous Office action, applicant states that this rejection will be addressed when there is an indication of allowable subject matter in the instant application.

7. Claims 37, 42, and 44-59, 61 and 63 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-46 and 50-53 of copending Application No. 09/083,585. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

a. This rejection is maintained for the reasons of record as set forth in the previous rejection mailed 5/24/00

b. In the response to the previous Office action, applicant states that this rejection will be addressed when there is an indication of allowable subject matter in the instant application.

8. Claims 37-59, 61, 63 and 64 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-36, 39-46, 50-53, 54

and 55 of copending Application No. 09/315,581. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of administration of an antisense nucleic acid therapeutic or diagnostic composition comprising the methods and medical device comprising administration of an antisense oligonucleotide that is not directed to an $A_1$ or $A_3$ adenosine receptor and is not contained in an expression vector wherein the sugar moiety of at least one nucleoside unit of said antisense oligonucleotide is not a 2'-deoxyribofuranosyl sugar moiety or at least one internucleotide linkage within said antisense oligonucleotide is not a phosphodiester or a phosphorothioate linkage of the instant invention is *encompassed by* the methods and medical device comprising administration of an antisense oligonucleotide that is not directed to an $A_1$ or $A_3$ adenosine receptor and is not contained in an expression vector of copending Application No. 09/315,581. This rejection is necessitated by applicant's amendments and additions to the claims in the response to previous Office action.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

a. In the response to the previous Office action, applicant states that the obviousness-type double patenting rejection over copending Application No. 09/315,581 will be addressed when there is an indication of allowable subject matter in the instant application.

***Claim Rejections - 35 U.S.C. § 112***

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

> person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 37-59, 61, 63 and 64 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for claiming **new matter**.

a. Claims 37-59, 61, 63 and 64 recite limitations to an antisense oligonucleotide that is not directed to an $A_1$ or $A_3$ adenosine receptor and is not contained in an expression vector. Applicant asserts that "[s]upport for the amendments can be found throughout the specification as originally filed, for example, on page 10."

b. Upon inspection, page 10 of the specification as filed is silent as to an antisense oligonucleotide that is not directed to an $A_1$ or $A_3$ adenosine receptor and the specification as filed appears to be silent as to an antisense oligonucleotide that is not directed to an $A_1$ or $A_3$ adenosine receptor and is not contained in an expression vector. In order to overcome the instant rejection, applicant must point, with particularity, as to where support for these new limitations may be found in the specification as filed.

***Claim Rejections - 35 U.S.C. § 102***

11. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

12. Claims 37, 38, 42, 44-59, 61, and 64 are rejected under 35 U.S.C. 102(e) as being anticipated by Unger et al., U.S. Patent No. 5,733,572. This rejection is necessitated by applicant's amendments and additions to the claims, as set forth in the response to the previous Office action.

a. Unger et al., U.S. Patent No. 5,733,572, at Figure 2, col. 1, lines 35-64, col. 3, lines 39-47, col. 4, lines 22-39, col. 7, lines 3-12, col. 19, lines 45-57, col. 22, lines 22-56, col. 31, lines 58-67, col. 32, lines 1-52, col. 40, lines 56-67, col. 41, lines 1-40, col. 49, lines 20-47, disclose methods of administration of an antisense nucleic acid therapeutic or diagnostic composition comprising the methods and medical device comprising administration of an antisense oligonucleotide that is RNA or DNA, and that is not directed to an $A_1$ or $A_3$ adenosine receptor and is not contained in an expression vector wherein the sugar moiety of at least one nucleoside unit of said antisense oligonucleotide is not a 2'-deoxyribofuranosyl sugar moiety or at least one internucleotide linkage within said antisense oligonucleotide is not a phosphodiester or a phosphorothioate linkage, wherein water or physiological saline used in the aerosol compositions of Unger et al. for therapeutic delivery directly into the lung would inherently comprise sterilized, pyrogen free water; and variations of the methods thereof; and nebulizers thereof.

13. Claim 59 is rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al., U.S. Patent No. 5,514,788. This rejection is necessitated by applicant's additions to the claims, as set forth in the response to the previous Office action.

a. Bennett et al., U.S. Patent No. 5,514,788, at col. 25, line 26-col. 17, line 44, disclose a method of modulating the expression of an ICAM-1 gene in mouse model comprising administering to said animal an antisense nucleic acid therapeutic or diagnostic composition comprising at least one antisense oligonucleotide or bioequivalent thereof, wherein said antisense oligonucleotide is not directed to an $A_1$ or $A_3$ adenosine receptor and is not contained in an expression vector. It is noted that claim 59 does not recite a limitation to aerosolizing an antisense oligonucleotide.

14. Claim 61 is rejected under 35 U.S.C. 102(b) as being anticipated by Nyce, WO 96/40266. This rejection is necessitated by applicant's amendments and additions to the claims, as set forth in the response to the previous Office action.

a. Nyce, at p. 17 line 27-p. 18, line 2, discloses a nebulizer for aerosolizing antisense oligonucleotides that would inherently constitute a device for pulmonary delivery of an aerosol comprising an antisense nucleic acid therapeutic or diagnostic composition comprising at least one antisense oligonucleotide or bioequivalent thereof, wherein said antisense oligonucleotide is not directed to an $A_1$ or $A_3$ adenosine receptor and is not contained in an expression vector. The specification as filed does not disclose how a device or nebulizer as claimed would differ in its mechanical structure from nebulizers known in the prior art. Applicant's do not argue as to how the nebulizers taught in the prior art could not be used to aerosolize a composition comprising an

antisense oligonucleotide directed to an $A_1$ or $A_3$ adenosine receptor and not contained in an expression vector.

***Claim Rejections - 35 U.S.C. § 103***

15. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

16. Claims 39-41, 43 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger et al., U.S. Patent No. 5,733,572, and each further in view of Milligan et al., Baker et al., U.S. Patent No. 5,789,573, Bennett et al., U.S. Patent No. 5,955,443, Dean et al., U.S. Patent No. 5,948,898, and Ravikumar et al. U.S. No. 5,554,746.

a. **Unger et al., U.S. Patent No. 5,733,572**, at Figure 2, col. 1, lines 35-64, col. 3, lines 39-47, col. 4, lines 22-39, col. 7, lines 3-12, col. 19, lines 45-57, col. 22, lines 22-56, col. 31, lines 58-67, col. 32, lines 1-52, col. 40, lines 56-67, col. 41, lines 1-40, col. 49, lines 20-47, disclose methods of administration of an antisense nucleic acid therapeutic or diagnostic composition comprising the methods and medical device comprising administration of an antisense oligonucleotide that is RNA or DNA, and that is not directed to an $A_1$ or $A_3$ adenosine receptor and is not contained in an expression vector wherein the sugar moiety of at least one nucleoside unit of said antisense oligonucleotide is not a 2'-deoxyribofuranosyl sugar moiety or at least one internucleotide linkage within said antisense oligonucleotide is not a phosphodiester or a phosphorothioate linkage, wherein water or physiological saline used in the aerosol compositions

of Unger et al. for therapeutic delivery directly into the lung would inherently comprise sterilized, pyrogen free water; and variations of the methods thereof; and nebulizers thereof.

b. Unger et al. does not teach methods for delivery of antisense oligonucleotides wherein the oligonucleotide comprises at least one nucleoside unit that is a 2'-O-substituted nucleoside unit, a 2'-O-alkoxyalkoxy substituent or a 2'-O-diakylaminooxyalkyl substituent, wherein at least one internucleotide linkage is 3'-methylenephosphonate and wherein the antisense oligonucleotide is ISIS 15839, ISIS 13312, ISIS 9605, ISIS 9606, ISIS 14859, ISIS 17709, ISIS 17044, ISIS 28089 or ISIS 104838.

c. **Milligan et al.**, at p. 1932, para 7-p. 1933, para 1, teach oligonucleotides wherein the sugar moiety of at least one nucleoside unit of said oligonucleotide is not a 2'-deoxyribofuranosyl sugar moiety and wherein the oligonucleotide comprise a 2'-O-substituted nucleoside unit, in order to enhance resistance to degradation.

d. **Baker et al., U.S. Patent No. 5,789,573**, at col. 3, lines 45-50, col. 4, lines 26-28, teach oligonucleotides that comprise a 2'-alkoxyalkoxy substituents in order to enhance the affinity of an antisense oligonucleotide for its target nucleic acid and more resistant to *in vitro* and *in vivo* degradation. teach oligonucleotides that comprise a 2'-O-alkoxyalkoxy substituent.

e. **Bennett et al., U.S. No. 5,955,443**, at col. 3, lines 15-18, col. 11, lines 36-65, teach oligonucleotides that comprise a 2'-O-diakylaminooxyalkyl substituent that is 2'-dimethylaminooxyethoxy in order to enhance the affinity of an antisense oligonucleotide for its target nucleic acid and more resistant to *in vitro* and *in vivo* degradation.

f. **Dean et al., U.S. Patent No. 5,948,898**, at Table 1, col. 2, lines 18-26, col. 8, lines 46-53, teach antisense oligonucleotides that are ISIS 9605 or ISIS 9606, which inhibit protein kinase C expression, are useful for reducing inflammation, and may be administered by inhalation.

g. **Ravikumar et al. U.S. No. 5,554,746**, at col. 2, lines 27-33 and 36-37, teach oligonucleotides that comprise at least one internucleotide linkage is 3'-methylenephosphonate in order to improve half life as well as membrane penetration.

h. It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have used methods of administration of a nucleic acid therapeutic or diagnostic composition comprising preparing, aerosolizing and introducing the composition into the lung of a mammal, wherein the composition comprises at least one oligonucleotide wherein at least one nucleoside unit is a phosphodiester, 2'-O-substituted nucleoside unit, a 2'-O-alkoxyalkoxy substituent or a 2'-O-diakylaminooxyalkyl substituent, wherein at least one internucleotide linkage is 3'-methylenephosphonate, and wherein the antisense oligonucleotide is ISIS 9605 or ISIS 9606.

i. One of ordinary skill in the art would have been motivated to have used methods of administration of a nucleic acid therapeutic or diagnostic composition comprising preparing, aerosolizing and introducing the composition into the lung of a mammal, wherein the composition comprises at least one oligonucleotide wherein at least one nucleoside unit is a 2'-O-substituted nucleoside unit, a 2'-O-alkoxyalkoxy substituent or a 2'-O-diakylaminooxyalkyl substituent, and wherein at least one internucleotide linkage is 3'-methylenephosphonate, in order to enhance

stability and cellular uptake of the oligonucleotide, as taught by the aforementioned prior art. One of ordinary skill in the art would have been motivated to deliver the antisense oligonucleotides ISIS 9605 or ISIS 9606 by methods of aerosolization, because Dean et al. discloses that said antisense oligonucleotides will reduce inflammation and may be inhaled.

***Conclusion***

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mark L. Shibuya (SRC)*, whose telephone number is (703) 308-9355, and/or to the patent analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.
19. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader* may be reached at (703) 308-0447.
20. Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is (703) 308-0196.

Mark L. Shibuya
Patent Examiner
Technical Center 1600
January 5, 2001